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APPLICANTS: Lapidus, et al.  
SERIAL NUMBER: 09/545,162 GROUP NUMBER: 1655  
FILING DATE: April 7, 2000 EXAMINER: Juliet C.  
Einsmann  
TITLE: METHODS FOR DETECTING NUCLEIC ACIDS  
INDICATIVE OF CANCER

Commissioner for Patents  
Washington, D.C. 20231

**AMENDMENT AND RESPONSE UNDER 37 C.F.R. § 1.115**

This paper is submitted in response to the Office Action mailed from the U. S. Patent and Trademark Office on May 22, 2001, in which claims were rejected under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 102(b) and (e). Applicants believe that not extension of time, or related fee, is required for entry of this paper. However, please consider this paper a conditional request for an extension of time, and any fee should be charged to deposit account number 20-0531. Reconsideration and withdrawal of the rejections are requested in light of the following amendments and remarks.

**AMENDMENTS**

Prior to further examination of this application, please amend the specification and claims as follows.

**In the Specification:**

On page 20, line 4, please add a paragraph that reads as follows. A red-lined version of this amendment is attached hereto.

A1  
Methods are provided for screening a patient for cancer or precancer by detecting the presence of nucleic acid fragments that are longer than nucleic acid fragments expected to be present in a sample obtained from a healthy individual. In one embodiment, a positive screen for cancer or precancer is identified when a patient tissue or body fluid sample comprising exfoliated cells or cellular debris contains an amount of nucleic acid of a length greater than about 200 base pairs that exceeds a predetermined amount.

**In the Claims:**

Please cancel claims 1 and 6 without prejudice. Please also amend claim 7 and add new claims 8 and 9 as follows. A red-lined version of the claims showing the claim amendments and the new claims is attached hereto

Sub 1  
A2  
~~7. (Amended) A method for screening a patient for cancer or precancer, the method comprising the step of  
detecting in a patient tissue or body fluid sample comprising exfoliated cells a nucleic acid fragment of a length that is greater than a length of a nucleic acid expected to be present in said sample in a healthy patient;  
the presence of said fragment being a positive screen for cancer or precancer.~~

Sub 2  
B2  
A3  
~~8. (New) A method for screening a patient for cancer or precancer, the method comprising the steps of:  
determining in a patient tissue or body fluid sample comprising exfoliated cells or cellular debris whether an amount of a nucleic acid greater than 200 base pairs in length exceeds a predetermined amount;  
identifying a positive screen for cancer or precancer if said amount does exceed said predetermined amount.~~

9. (New) A method for screening a patient for cancer or precancer, the method comprising the steps of:

determining in a patient tissue or body fluid sample comprising exfoliated cells or cellular debris a first amount of long nucleic acid of a length greater than 200 base pairs;

A3  
determining in said sample a second amount of nucleic acid of a length less than said long nucleic acid;

determining a ratio between said first amount and said second amount; and identifying a positive screen for cancer or precancer if said ratio exceeds a

threshold ratio for patients who do not have cancer or precancer.

### **REMARKS**

#### **Objection to the Specification**

The abstract was objected to for not containing an adequate description of the claimed invention. The abstract has been amended to include a further description of the claimed invention. Support for this amendment can be found throughout the Specification including the claims as originally filed. For example, support can be found at least at page 11, line 27, through page 12, line 7 of the Specification. Applicants believe the this amendment introduces no new matter. Accordingly, Applicants respectfully request that the objection be reconsidered and withdrawn.

#### **Rejections of the Claims**

Claims 1-7 were considered. Claims 6 and 7 were rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Claims 1, 2, and 7 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ditkoff, et al. (Surgery 120: 959-965, 1996) (hereafter, "Ditkoff"). Claims 1, 3, 4, 5, and 7 were rejected under 35 U.S.C. § 102(b) as being anticipated by Smith-Ravin, et al. (Gut 36:81-86, 1995) (hereafter, "Smith-Ravin"). Claims 1, 4, 5, 6, and 7 were rejected under 35 U.S.C. § 102(e) as being anticipated by Schiff, et al. (U.S. Patent No. 5,942,396) (hereafter "Schiff").

Upon entry of the present amendments, claims 2-5, and 7-9 are pending in this application. The claims are amended to further clarify the claimed subject matter. Claims 1 and 6 are canceled without prejudice and without any intention to abandon the subject matter as filed, but with the intention that claims of the same, greater, or lesser scope may be pursued in this or a continuing application. Support for the amendments to claim 7 and for new claims 8 and 9 is found throughout the specification and in the claims as originally filed. For example, support can be found at least at page 11, line 18, through page 12, line 18 of the Specification. Applicants believe that the claim amendments introduce no new matter.

### **I. Claim Rejections Under 35 U.S.C. § 112 Second Paragraph**

Claims 6 and 7 were rejected under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants have canceled claim 6, and amended claim 7 to clarify that a positive screen for cancer or precancer is identified when a nucleic acid fragment longer than a nucleic acid expected to be found in a healthy patient is detected. Applicants also submit that the rejections under 35 U.S.C. § 112, second paragraph, should not be maintained over new claims 8 and 9. Therefore, Applicants respectfully request that the rejections under 35 USC 112 be reconsidered and withdrawn.

### **II. Claim Rejections Under 35 U.S.C. § 102**

#### **A. Rejection of claims 1, 2, and 7 as anticipated by Ditkoff**

Claims 1, 2, and 7 were rejected under 35 USC § 102(b) as anticipated by Ditkoff. Claim 1 has been canceled without prejudice and claim 7 has been amended to clarify that a positive screen for cancer or precancer is identified when a nucleic acid fragment longer than a nucleic acid expected to be found in a healthy patient is detected. Accordingly, Applicants traverse this rejection to the extent that it is maintained over the claims as amended.

Applicants respectfully submit that Ditzkoff discloses a method that involves detecting the presence of a specific transcript (the thyroglobulin transcript) in order to detect the presence of circulating malignant thyroid cells in a blood sample. However, Ditzkoff fails to teach or suggest a method for detecting cancer or precancer based solely on the length, as opposed to the identity, of a nucleic acid present in a patient tissue or body fluid sample containing exfoliated cells or cellular debris. Ditzkoff also fails to disclose a method based on an analysis of an amount of nucleic acid longer than 200 base pairs in such a sample. The Office Action points to the 529 bp fragment disclosed in Fig. 2A of Ditzkoff. However, Applicants respectfully submit that the method in Ditzkoff is based on detecting the presence of the thyroglobulin transcript versus an absence of the thyroglobulin transcript as indicated in the legend of Fig. 2A. Accordingly, Ditzkoff fails to specifically teach or suggest a method based on detecting the presence of a nucleic acid that is longer than a nucleic acid expected to be in a healthy patient, or determining whether an amount of nucleic acid longer than 200 base pairs exceeds a predetermined amount. Similarly, Ditzkoff fails to specifically teach or suggest determining a ratio between an amount of nucleic acid longer than 200 base pairs and an amount of shorter nucleic acid.

Accordingly, Applicants respectfully submit that Ditzkoff fails to disclose every element of the amended claims and cannot form the basis for continued rejection under 35 U.S.C. § 102. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

*B. Rejection of Claims 1, 3, 4, 5, and 7 as anticipated by Smith-Ravin*

Claims 1, 3, 4, 5, and 7 were rejected under 35 USC § 102(b) as anticipated by Smith-Ravin. Independent claim 1 has been canceled without prejudice, and independent claim 7 has been amended to clarify that that a positive screen for cancer or precancer is identified when a nucleic acid fragment longer than a nucleic acid expected to be found in a healthy patient is detected. Accordingly, Applicants traverse this rejection to the extent that it is maintained over the claims as amended.

Applicants respectfully submit that Smith-Ravin discloses detecting the presence of specific point mutations (mutations at the first and second based of codon 12 of the *ras* gene) as

disclosed in the second column on page 83 of Smith-Ravin. In addition, these point mutations are detected by amplifying fragments 161 bp and 146 bp, respectively. Accordingly, Smith-Ravin fails to teach or suggest a method based on a determination of an amount of nucleic acid longer than 200 base pairs in a patient tissue or body fluid sample containing exfoliated cells or cellular debris. In addition, Smith-Ravin fails to teach or suggest a method for detecting cancer or precancer based solely on the length, as opposed to the identity, of a nucleic acid present in such a sample. Therefore, Applicants respectfully submit that Smith-Ravin fails to specifically teach or suggest a method based on detecting the presence of a nucleic acid that is longer than a nucleic acid expected to be in a healthy patient, or determining whether an amount of nucleic acid longer than 200 base pairs exceeds a predetermined amount. Similarly, Smith-Ravin fails to specifically teach or suggest determining a ratio between an amount of nucleic acid longer than 200 base pairs and an amount of shorter nucleic acid.

Accordingly, Applicants respectfully submit that Smith-Ravin fails to disclose every element of the amended claims and cannot form the basis for continued rejection under 35 U.S.C. § 102. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

C. Rejection of Claims 1, 4, 5, 6, and 7 as anticipated by Schiff

Claims 1, 4, 5, 6, and 7 were rejected under 35 U.S.C. § 102(e) as anticipated by Schiff. Independent claims 1 and 6 have been canceled without prejudice, and independent claim 7 has been amended to clarify that a positive screen for cancer or precancer is identified when a nucleic acid fragment longer than a nucleic acid expected to be found in a healthy patient is detected. Accordingly, Applicants traverse this rejection to the extent that it is maintained over the claims as amended.

Applicants respectfully submit that Schiff discloses a method for screening a patient for colorectal neoplasia by analyzing the extent of apoptosis in a biopsy sample. However, Schiff fails to teach or suggest a method based on a determination of an amount of nucleic acid longer than 200 base pairs in a patient tissue or body fluid sample containing exfoliated cells or cellular

debris. In addition, Schiff fails to teach or suggest a method for detecting cancer or precancer based solely on the length, as opposed to specific characteristics, of nucleic acid present in such a sample. Page 4 of the Office Action states that Schiff teaches "electrophoretic methods including the isolation of cellular DNA and separation by gel electrophoresis to determine the extent of DNA fragmentation." The Office Action further states that "such a method would inherently involve determining the ratio of DNA molecules larger than 200 bases pairs to the ratio of DNA molecules smaller than 200 base pairs." However, Applicants respectfully submit that the electrophoretic methods disclosed in Schiff involve determining the presence of "a characteristic laddering of multiples of 180 bp fragments." See column 6, lines 18-21, of Schiff. Therefore, Applicants respectfully submit that Schiff fails to specifically teach or suggest a method based on detecting the presence of a nucleic acid that is longer than a nucleic acid expected to be in a healthy patient, or determining whether an amount of nucleic acid longer than 200 base pairs exceeds a predetermined amount. Similarly, Schiff fails to specifically teach or suggest determining a ratio between an amount of nucleic acid longer than 200 base pairs and an amount of shorter nucleic acid.


Accordingly, Applicants respectfully submit that Schiff fails to disclose every element of the amended claims and cannot form the basis for continued rejection under 35 U.S.C. § 102. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

**CONCLUSION**

Applicants submit that claims 2-5 and 7-9 are in condition for allowance and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned agent of record.

Respectfully submitted,

Dated: August 22, 2001



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